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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/465,133	12/15/99	VEGEO	E 213/103

EXAMINER	
DRAPIK, S	
ART UNIT	PAPER NUMBER
1633	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	09/465,133	VEGEO ET AL.	
	Examiner	Art Unit	
	Deborah Clark	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *100-105,107,108,111-123,127 and 129-143* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *100-105,107,108,111-123,127 and 129-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Christopher Drabik, Group Art Unit 1633

Applicants response to the Restriction Requirement mailed 5/08/01, as Paper No. 10, has been received and filed on 7/11/01 as Paper No 11. Claims 106, 109, 110, 124-126 and 128 have been cancelled. Claims 100-104, 111, 123 , 129, 133 and 134 have been amended. Claims 135-143 have been added as new claims. Applicants have elected Group I without traverse. The Restriction Requirement has therefore been made **FINAL.**

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 100-105,107, 108, 111-123, 127, 129-135 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements involve the relation of the method of regulating expression to the transgenic animal and further the relation between the first and second nucleic acid cassettes. Claim 100 is drawn to a method of regulating expression of a desired gene in an animal. The claim recites a method followed by the recitation of an animal

comprising two elements, a first and second nucleic acid cassette, (a) and (b) . As the claim is written, it is unclear how the claimed method recited in the preamble relates to either of the elements (a) or (b). The claim recites a method and further "wherein said animal contains." The relevance of the method to the recited animal is not distinctly delineated because it is unclear whether the nucleic acid cassettes are or are not regulated by the ligand administered to the animal. It is further unclear in part (a) what might be the purpose of transcribing a promoter. At line 9 of claim 135 the claim reads "...a mutated receptor protein which regulates the transcription of a molecular switch promoter..." Promoters are generally not transcribed in eukaryotic cells, but rather drive the transcription of an associated gene. Claims 102-105,107, 108, 111-123, 127, 129-135 are also rejected under 35 USC 112, 2nd paragraph because they depend from claim 100 and are, therefore, bound to the limitations of claim 100.

Claims 135-143 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. Claim 135 reads "A method...comprising: administering to an animal a pharmacologic dose that activates a molecular switch...and results in regulated expression of a desired gene..." As the claim is written essential elements are missing involving the bridge between "activation" and "regulation." It is unclear how the two elements are related. For example, it is not apparent that regulated expression is or is not dependent upon "activation" of the molecular switch. Claim 135 is further unclear because the use of the term "capable" at

line 6 does not distinctly set forth the metes and bounds of the claimed subject matter. "Capable" suggests the possibility of an event occurring, but does not clearly point out the probability of that event occurring. Hence, it is not clear whether the ligand binding domain is or is not activated by the administration of a ligand. Claims 136-143 are also rejected under 35 USC 112, 2nd paragraph because they depend from claim 135 and are, therefore, bound to the limitations of claim 100.

Claims 100-105,107, 108, 111-123, 127, 129-143 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 100 and 135 employ the use of the term "molecular switch" to define an essential element of the invention, however, it is not clear that the use of the term is consistent between claims 100 and 135. In claim 100, the use of the term "molecular switch" apparently denotes a nucleic acid sequence comprising a promoter. In claim 135, it is ambiguous as to whether molecular switch refers to a nucleic acid sequence or a protein (steroid hormone receptor). In claim 100 the molecular switch appears to be involved in the transcription through a nucleic acid regulatory element, whereas, in claim 135, the molecular switch appears to be encoded in a protein (see lines 3 and 4 of claim 135). Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 100-105,107, 108, 111-123, 127, 129-143 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The instant application lacks written description for claimed subject matter encompassed by the term "desired gene" , or, alternatively, "desired protein".The specification fails to describe the genus of "desired genes" or "desired proteins" encompassed in the claims with particularity to indicate that Applicants had possession of the claimed invention. As an adjunct to the lack of description for desired proteins or genes, the animals encompassed by the claims lack written description in that no phenotypes associated with "desired genes" or "desired proteins" have been disclosed. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification

and which are not conventional in the art **as of Applicants effective filing date**. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiments of any and all desired genes, desired proteins and resultant phenotypes lack written description. The skilled artisan cannot envision the detailed structure and phenotypic effect of the nucleic acid constructs, genes, and/or proteins of all of the encompassed claimed embodiments and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims100-105,107, 108, 111-123, 127, 129-143 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 100-105,107, 108, 111-123, 127, 129-143, are broadly drawn to encompass any and all mutations to steroid receptors such that said mutated receptors are capable of binding ligands which are not "naturally occurring." As pointed out above, possession may be shown by actual reduction to practice, clear depiction of the

invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Regarding the claim to any and all mutations in steroid receptors, the applicants have clearly not delineated a representative number of mutations of the genus of receptor mutations involving the ability to bind any and all non-naturally occurring ligands such that possession of the claimed invention would be apparent to one of skill in the art. While the applicants have generated mutations in the progesterone receptor such that the mechanism of RU38486 has been altered it is not apparent what other mutations, steroid hormone receptor ligand binding domains and ligands are encompassed by disclosure. One of skill in the art would not be able to envision any and all mutations in any and all steroid receptors which function as claimed, and hence the disclosure lacks written description for the genus of mutated steroid hormone receptor.

Claims 100-105,107, 108, 111-123, 127, 129-143 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 100-105,107, 108, 111-123, 127, 129-143 are broadly drawn to encompass animals comprising a mutated steroid hormone receptor transgene and a second transgene activated by the binding of the modified receptor protein. Said receptor protein ligand binding domain is "distinct from naturally occurring ligand binding

domains". The animals encompassed in the claims include those which contain episomal versions of the transgenes, as well as animals genetically modified to contain the genes either through germline modification or by transduction with, e.g. a viral vector. Further, the gene driven by the modified receptor is not recited in the claims and hence could be any gene known to man or indeed any nucleic acid without a known function.

While the applicants claims encompass a transgenic animal comprising a gene which is capable of being regulated, applicants do not provide any means for discerning what sort of phenotype might be involved in any gene regulated by the mutated receptor. Indeed, applicants have not even provided evidence of a marker gene such as luciferase functioning in a transgenic animal in a manner consistent with the claimed scope of the invention. For the invention to function as claimed, at least two genes must be introduced into an animal. The first being the mutated receptor, and the second being the receptor driven reporter gene. The breadth of the claims encompasses any modified receptor, DNA binding sequence, transcriptional regulatory element and any gene. Applicants have prospectively suggested one mutated receptor which might function, but have neither disclosed nor recited any particular phenotype caused by transformation of an animal and have not demonstrated an animal which has a phenotype which may be modulated by a molecular switch protein.

While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic mammals comprising a transgene of interest; it is not predictable if the transgene would be expressed at a level and specificity sufficient to

cause a particular phenotype. For instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic mammals are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. Without significant guidance regarding these elements and in the absence of any descriptive phenotype, it would be unclear to one of skill in the art how to reproduce the invention as claimed.

In regard to the general unpredictability of generating a transgenic animal, Wall (Theriogenology, 1996) states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1994) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); *e.g.*, specific promoters, presence or absence of introns, *etc*

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is specifically supported by Hammer et al. (Journal of Animal Science, 1986) who report the production of transgenic mice, sheep and pigs; however only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human

growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. See also Ebert et al. (Molecular Endocrinology, 1988). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins et al. state that "a given construct may react very differently from one species to another." See page S39,

Regarding the generation of transgenic animals by means of somatic cell transformation (i.e. infection by a viral vector or through the use of non-integrating plasmids.) The use of viral vectors for the transformation of animals in vivo is beset with problems which include appropriate vector design, which affords the ability to sufficiently transduce enough cells and obtain adequate levels of transgene expression, the significant problem of avoiding host immune response when viral proteins are involved and the avoidance of gene silencing events once the cells have been transduced. All of these factors have proven to often be case specific, not easily circumvented, and require more than routine experimentation to overcome. In the case of transformation by non-integrating constructs, a major concern is the transience of gene expression associated with episomal gene vectors. Applicants have not provided any guidance, either prospectively or in the form of working examples suggesting how the foregoing difficulties might be overcome such that one of skill in the art might readily be able to practice embodiments of the claimed invention associated with somatic cell transformation of animals.

Regarding the general ability to generate modified steroid hormone receptors with altered ligand binding characteristics and the ability to modulate gene function in general: The inventions as disclosed rests upon the ability to adequately change the ligand binding characteristics of a given receptor such that it becomes desensitized to endogenous signaling molecules and conversely become sensitive to a new ligand. This presupposes that the folding characteristics of a new ligand binding domain can be easily and readily predicted and crafted to function with any desired signaling molecule. It is well known in the art that the problem of predicting the three dimensional structure of a protein solely based upon primary amino acid sequence is not a trivial consideration. While the structure of a potential ligand may be well known and from the structure of this molecule a complementary binding conformation deduced the appropriate three dimensional conformation of the ligand binding domain does not necessarily follow. In other words, given a known ligand, the design of an appropriately folded binding pocket consisting of the correct amino acids requires more than good ideas, but rather trial and error experimentation to generate a construct of the desired activity.

Considering the nature of the invention, the scope of the claims, the state of the prior art, the degree of guidance provided and the lack of working examples, it would not be possible for one of skill in the art to practice the invention as claimed. Claims 100-105,107, 108, 111-123, 127, 129-143 are rejected as lacking enablement under 35 USC 112, 1st paragraph.

Conclusions

No claim of the instant application has been allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Drabik whose telephone number is 703-605-1156. The examiner can normally be reached on Monday-Friday from 9am to 5pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on 703- 305-4051. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Inquiries of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234. Questions regarding review of formality issues may be directed to Kim Davis, the patent analyst assisting in this application. She may be reached at 703-305-3015.

Deborah Clark

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